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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/034,278	12/28/2001	Ronald T. Kurnik	50225-8032.US03	9825

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EXAMINER	
BARTON, JEFFREY THOMAS	
ART UNIT	**PAPER NUMBER**
1753	

DATE MAILED: 05/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,278	KURNIK ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Barton	1753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7 and 11-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7 and 11-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040830*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment filed on 22 February 2005 does not place the application in condition for allowance.

Status of the Objections and Rejections Pending Since the Office Action of 20 September 2004

2. The objections to the Specification are withdrawn due to Applicants' amendment.

3. All objections and rejections of claims 2, 3, and 8-10 are withdrawn due to the cancellation of the claims.

4. The rejections of claims 1, 4-7, and 14-24 under 35 U.S.C. §103(a) as unpatentable over Manz et al in view of Křivánková et al is maintained.

5. The rejection of claims 11 and 12 under 35 U.S.C. §103(a) as unpatentable over Manz et al in view of Křivánková et al and Ramsey is maintained.

6. The rejection of claims 1 and 13 under 35 U.S.C. §103(a) as unpatentable over Fuchs et al in view of Křivánková et al and Manz et al is maintained.

7. All rejections made under the judicially created doctrine of obviousness-type double patenting over Application No. 09/780,638 (Now U.S. Patent No. 6,818,113) are withdrawn due to the acceptance of the terminal disclaimer filed by the Applicants with this amendment.

Terminal Disclaimer

8. The terminal disclaimer filed on 22 February 2005 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,818,113 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 103

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 1, 4-7, and 14-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Manz et al in view of Křivánková et al.

Relevant to claim 1, Manz et al disclose a method for injecting a sample comprising a plurality of charged components and separating the components by electrophoresis in a microfluidic device (Column 1, lines 6-10; Column 2, lines 60-66), wherein said microfluidic device (Figures 1 and 3) includes a separation channel (22), having an upstream portion terminating in an upstream reservoir (R) and a downstream portion terminating in a downstream reservoir (W), sample and drain channels (23 and 24) intersecting the separation channel between the two channel portions at first and second junctions (25 and 26), respectively, and terminating in sample and drain reservoirs (S and D), respectively; and said device further includes electrodes in contact with the fluid in each said reservoir, including an upstream electrode, a downstream

electrode, a sample electrode, and a drain electrode (Column 4, lines 4-10); the method comprising: a) placing into said separation channel, side channels and drain reservoir a first electrolyte solution (Column 3, line 66 - Column 4, line 3; Column 5, lines 35-38); b) placing into said sample reservoir the sample solution; c) creating a first voltage gradient between said sample electrode and said drain electrode, such that the charged components move into said separation channel (Column 5, lines 38-43), with the upstream and downstream electrodes being in a floating state during this step (Column 5, lines 43-47); and d) placing said sample and drain electrodes in a floating state, and creating a second voltage gradient between said downstream and upstream electrodes, such that the charged components move through the separation channel and separate into discrete bands according to their electrophoretic mobilities. (Column 5, lines 48-58; "switched off" would correspond to the definition of "floating" given at page 11, lines 15-19 of the applicants' specification)

Also relevant to claim 1, Manz et al disclose the advantageousness of sample stacking within a prior art electrophoresis method. (Column 1, lines 48-51)

Relevant to claims 4 and 5, Manz et al disclose the sample and drain channels intersecting the separation channels at either directly opposed junctions or at staggered junctions. (Column 4, lines 42-51)

Relevant to claim 6, Manz et al disclose the sample channel (23) being upstream of the drain channel (24). (Figure 3)

Manz et al do not explicitly disclose a method in which the sample solution and background electrolyte are chosen such that the first and second electrolyte solutions each comprise an ion having lower mobility in an electric field than any of said charged components, and one or the other of said electrolyte solutions comprises an ion having higher mobility in an electric field than any of said charged components, nor do they explicitly disclose the injection step including sample stacking within a region of said separation channel. (Claim 1)

Relevant to claim 1, Křivánková et al disclose a method of sample stacking in capillary electrophoresis (Section 5, Sample induced transient ITP in CZE; further discussion on pages 31-33) in which the sample solution and background electrolyte are chosen such that the first (background) and second (sample) electrolyte solutions each comprise an ion having lower mobility in an electric field than any of said charged components (B in figure 24), and one or the other of said electrolyte solutions comprises an ion having higher mobility in an electric field than any of said charged components (A in figure 24), which is present in a higher concentration than said charged components. (e.g. Figure 23 (b) and (c); 100-300 mM NaCl with 0.1 mM sample) The stacking occurs due to isotachophoresis (Transient ITP; Section 5), and will result in increased sample concentration (i.e. "into a small volume"), as shown in Figure 23 and discussed in the paragraph bridging the 1st and 2nd columns of page 29 - "sharp peaks" indicates a narrow sample band, with a corresponding smaller volume.

Relevant to claims 14 and 15, Křivánková et al disclose within their method the use of negatively charged sample components and chloride as the higher mobility ion (Figure 23)

Relevant to claim 16, Křivánková et al disclose the use of imidazole as the low-mobility ion with negatively charged analytes. (Table 3)

Relevant to claims 17 and 18, Křivánková et al disclose the low-mobility ion having a concentration of 10 mM in a separation. (Figure 23)

Relevant to claims 19 and 20, Křivánková et al disclose analysis of charged sample components having a concentration of 0.1 μM. (Figure 21)

Relevant to claims 21 and 22, Křivánková et al disclose the high-mobility ion having a concentration of 3-20 mM (Table 2), and also show experiments where its concentration ranges from 0-300 mM. (Figure 23)

Relevant to claim 23, Křivánková et al disclose a method in which only the first (i.e. leading) electrolyte solution comprises the high mobility ion. (Figure 18) This leading electrolyte also served as the background electrolyte for capillary zone electrophoresis.

Relevant to claim 24, Křivánková et al disclose a method in which only the second (i.e. sample) electrolyte solution comprises the high mobility ion. (Section 5)

Addressing claim 1, it would have been obvious to one having ordinary skill in that art at the time the invention was made to modify the method of Manz et al by using samples and electrolytes that would provide sample stacking upon injection and electric

field application, as taught by Křivánková et al, because Manz et al described such stacking as advantageous for electrophoretic separations (Column 1, lines 48-51), and Křivánková et al teach the advantages of using such isotachophoretic stacking methods in capillary electrophoresis methods, in that it allows increased sensitivity and analysis speed. (Conclusions) The use of electrokinetic injection as described in the method of Manz with such a sample as described by Křivánková et al would lead to a degree of isotachophoretic sample stacking within the separation channel in the injection step. (i.e. step (c) of the instant claim)

Addressing claim 7, it would also be obvious to use the downstream side channel as the sample source, and the upstream side channel as the drain, because it would be equally effective in transferring sample into the separation channel, and in the case of positively charged analytes, it would facilitate sample stacking in the appropriate direction. (i.e. the direction of the electric field in the separation channel during injection would be the same as that during separation)

Addressing claims 14-24, examples of electrolytes and suitable concentrations from Křivánková et al, referenced to instant claims, are given above. Any would be obvious to use in a combined method.

11. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Manz et al and Křivánková et al as applied to claim 1 above, and further in view of Ramsey. (US 6,342,142)

Manz et al and Křivánková et al disclose a combined method as described above in addressing claim 1.

Neither Manz et al nor Křivánková et al explicitly disclose a method wherein the charged components are selected from the group consisting of nucleic acids, proteins, polypeptides, polysaccharides, and synthetic polymers (Claim 11); or a method of claim 11 wherein said charged components comprise nucleic acids. (Claim 12)

Ramsey discloses a method wherein the sample comprises nucleic acids. (Column 20, lines 35-36)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use the combined method of Manz et al and Křivánková et al to analyze samples comprising nucleic acids, because such capillary electrophoretic methods provide excellent resolution of mixtures of charged molecules. (See Manz et al, Background and Summary sections; numerous cited examples in Křivánková et al) Furthermore, it would have been within the level of ordinary skill in the electrophoresis art to select a suitable analyte from materials (such as nucleic acids) which were well known as being separable by electrophoretic methods.

12. Claims 1 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fuchs et al in view of Křivánková et al and Manz et al.

Fuchs et al disclose a method for injecting a sample comprising a plurality of charged components and separating the components by electrophoresis in a microfluidic device (Column 4, lines 24-38), wherein said microfluidic device (Figures 1a

and 1b) includes a separation channel (20), having an upstream portion terminating in an upstream reservoir and a downstream portion terminating in a downstream reservoir (Both reservoirs labeled 16), sample and drain channels intersecting the separation channel between the two channel portions at first and second junctions, respectively, and terminating in sample and drain reservoirs (24 and 26), respectively; and said device further includes electrodes in contact with the fluid in each said reservoir (Column 20, lines 61-63), including an upstream electrode, a downstream electrode, a sample electrode, and a drain electrode; the method comprising: a) placing into said separation channel, side channels and drain reservoir a first electrolyte solution (Column 20, lines 53-56; necessary for electrokinetic motion); b) placing into said sample reservoir the sample solution (Column 20, lines 56-59); c) creating a first voltage gradient between said sample electrode and said drain electrode (Column 15, lines 52-62; Column 20, lines 56-63), such that the charged components move into said separation channel; and d) creating a second voltage gradient between said downstream and upstream electrodes, such that the charged components move through the separation channel and separate into discrete bands according to their electrophoretic mobilities. (Column 16, lines 15-52)

Also relevant to claim 1, Fuchs et al disclose isotachophoretic concentration of a sample within their electrophoresis method. (Column 23, lines 48-53)

Relevant to claim 13, Fuchs et al disclose a method wherein the charged components comprise labeled molecules having distinct and characterized electrophoretic mobilities (Column 23, lines 29-53; Column 26, lines 19-53), said

molecules having been cleaved from molecular species with biological or chemical recognition properties in the course of a multiplexed chemical or biochemical assay (Column 23, line 29 - Column 24, line 47)

Fuchs et al do not explicitly disclose a method in which the sample solution and background electrolyte are chosen such that the first and second electrolyte solutions each comprise an ion having lower mobility in an electric field than any of said charged components, and one or the other of said electrolyte solutions comprises an ion having higher mobility in an electric field and higher concentration than any of said charged components, nor do they explicitly disclose the injection step including sample stacking within a region of said separation channel.

Fuchs et al also do not explicitly disclose placing the upstream and downstream electrodes in a floating state during the injection step or placing said sample and drain electrodes in a floating state concurrently with application of the potential between upstream and downstream electrodes.

Křivánková et al disclose a method of sample stacking in capillary electrophoresis (Section 5, Sample induced transient ITP in CZE; further discussion on pages 31-33) in which the sample solution and background electrolyte are chosen such that the first (background) and second (sample) electrolyte solutions each comprise an ion having lower mobility in an electric field than any of said charged components (B in figure 24), and one or the other of said electrolyte solutions comprises an ion having

higher mobility in an electric field than any of said charged components (A in figure 24), which is present in a higher concentration than said charged components. (e.g. Figure 23 (b) and (c); 100-300 mM NaCl with 0.1 mM sample) The stacking occurs due to isotachophoresis (Transient ITP; Section 5), and will result in increased sample concentration (i.e. "into a small volume"), as shown in Figure 23 and discussed in the paragraph bridging the 1st and 2nd columns of page 29 - "sharp peaks" indicates a narrow sample band, with a corresponding smaller volume.

Manz et al disclose a similar microfluidic device in which they carry out an injection method comprising the steps of placing the upstream and downstream electrodes in a floating state while applying a voltage to inject a sample (Column 5, lines 43-46), and placing said sample and drain electrodes in a floating state concurrently with application of the potential between upstream and downstream electrodes. (Column 5, lines 48-58)

It would have been obvious to one having ordinary skill in that art at the time the invention was made to modify the method of Fuchs et al by using samples and electrolytes that would provide sample stacking upon injection and electric field application, as taught by Křivánková et al, because it requires a simpler electrolyte system than typical isotachophoretic methods, Fuchs et al described using isotachophoretic stacking within their method (Column 23, lines 48-53), and Křivánková et al teach the advantages of using such isotachophoretic stacking methods in capillary

electrophoresis methods, in that it allows increased sensitivity and analysis speed. (Conclusions) Furthermore, the use of electrokinetic injection would lead to a degree of sample stacking within the separation channel in the injection step. (i.e. step (c) of the instant claim)

It would also have been obvious to allow the electrodes in the upstream and downstream reservoirs to float during injection and to allow the electrodes in the sample and waste reservoirs to float after injection, as taught by Manz et al, because it provides the simplest method of injection and separation. (i.e. only applying a potential to two electrodes at a time) Furthermore, since Fuchs is silent concerning the specifics of the injection procedure, a skilled artisan would look to the teaching of other prior art methods (e.g. Manz et al) for suitable methods. As Manz et al teach the effectiveness of their injection method, it would have been obvious to use it.

Response to Arguments

13. Applicant's arguments filed 22 February 2005 have been fully considered but they are not persuasive.

Regarding the combination of Manz et al with Křivánková et al, (Amendment, Pages 7-8), Applicant argues that the "method of Manz et al" would be understood to be the pushback strategy described in the reference. (Page 9, 2nd full paragraph) This does not change the fact that Manz et al teach the limitations cited in the rejection, and fails to persuade. Applicant further argues that no advantage of stacking is taught by Manz et al, and that Křivánková et al point to risks within their isotachophoretic method.

(Page 9, 3rd full paragraph) The Examiner maintains that the cited passage in Manz et al (Column 1, lines 48-51), while obviously not teaching a detailed stacking procedure, does show that Manz et al viewed sample preconcentration/stacking as an advantage, which provides a degree of motivation for incorporating stacking procedures, such as those described by Křivánková et al. Also, far from teaching away from using isotachophoretic stacking procedures, Křivánková et al teach their benefits - see the Conclusion section. The passage cited by Applicants (Page 31, 1st and 2nd columns) amount to warnings to use care in performing the procedures, not suggestions to avoid the procedures entirely. Applicants then argue that the stacking mentioned by Manz et al would not be by isotachophoresis, and that the combination of references would not address the leakage problem described by Manz et al. (Amendment Page 9, 4th and 5th full paragraphs) The Examiner agrees that Manz et al do not teach isotachophoresis - Křivánková et al were relied upon for this teaching. Additionally, the methods Manz et al use in addressing leakage are not relevant to the instant claims at all. This combination does not destroy the methods Manz et al use to address leakage, therefore rendering the argument unpersuasive.

Regarding the rejections further relying upon Ramsey, Applicants' arguments focus on the patentability argued against the rejection of claim 1, and describe Ramsey as also distinct from the claimed methods. (Amendment Page 10, Section III) Ramsey is relied upon to teach the choice of analytes - not specific methods of injection or analysis. Therefore, Applicants' arguments are unpersuasive.

Regarding the rejections based on Fuchs et al in view of Křivánková et al and Manz et al, Applicant argues that Křivánková et al do not teach that their method enhances the simplicity of a separation process, as they mention the complex conditions required for sample induced stacking. (Amendment , Page 11, 5th full paragraph) However, since the sample induced stacking shown by Křivánková et al uses a homogeneous buffer in the channel system (i.e. separate terminating/leading electrolytes do not need to be filled beforehand), in this aspect, sample induced stacking is simpler. Applicant further argues that Manz et al teach away from allowing the sample and waste reservoirs to float after injection. (Amendment, Page 11, 6th full paragraph) At Column 5, lines 48-56, Manz et al describe using this exact method. As far as the leakage problem described by Manz et al is concerned, they disclose a method of addressing it without application of a potential to the sample and waste reservoirs in the embodiment of Figure 4 (See Column 6, lines 40-62). Therefore, Manz et al is not considered to teach away from this method. Finally, Applicant Argues that Fuchs et al do not disclose using isotachophoresis in a separation method, but only as a means of mixing materials. (Amendment, Paragraph bridging pages 11 and 12 - 3rd full paragraph of Page 12) Fuchs was not relied upon to teach the isotachophoretic injection method - this was disclosed by Křivánková et al, along with description of its various advantages. The performance of isotachophoretic methods by Fuchs et al in their device is considered to provide a suggestion for using other isotachophoretic methods as well, such as those taught by Křivánková et al. Therefore, Applicants' arguments are not persuasive.

For these reasons and those presented above in the rejections, the Examiner maintains that the instant claims are obvious over the prior art of record.

Conclusion

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Jeffrey Barton, whose telephone number is (571) 272-1307. The examiner can normally be reached Monday-Friday from 8:30 am – 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nam Nguyen, can be reached at (571) 272-1342. The fax number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

JTB
May 6, 2005

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